EICHHORST (H.)

RECENT CLINICAL NOTES

ON

KRYOFINE,

(Methoxacet-p-phenetidin.)

BY

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KRYOFINE. A NEW ANTIPYRETIC.

BY

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The Privat-docent of chemistry of this place, Dr. Bischler, has for years studied the theory of fever remedies and as can readily be understood his studies have led him to evolve a series of antipyretics which should meet his views. As in the first instance, only purely scientific questions were concerned, I have gladly granted the request of Dr. Bischler to test the practical application of these drugs at the bedside. In this manner a whole series of remedies has passed through my hands in the course of several years, of which a few would be quite capable of causing serious competition to the newer antipyretics.

It is not my intention to give a resumé in the following of all my experiences, but I shall return later on to this subject which obviously is of great theoretical and practical importance. For the present may it suffice to point out one of these drugs which seems to me **on account of its certain antipyretic action even in small doses and the generally complete absence of unpleasant collateral effects** to be very well suited to be introduced into medical practice.

In order to avoid misunderstanding let it be specially remarked that we have not indeed applied the drug in question because we consider a reduction of increased body-temperature an absolutely worthy aim of the physician; on the contrary, we only very rarely make use of antipyretics at the Zurich Clinic, and deviated from this precept merely to find occasion to test the drug.

*The translator has endeavored to retain the author's style as much as possible and to make the English version virtually literal, believing this to be an interesting feature of the report.

The name **Kryofine** is of course chosen only for the sake of simplicity. According to its chemical composition the drug represents Methoxacet-p-phenetidin. The considerations which caused Dr. Bischler to expect a temperature reducing action from this drug in particular, I give in the original words of the discoverer.

"Kryofine is, like phenacetin, a p-phenetidin derivative, and indeed it is the condensation product from phenetidin and methoxyacetic acid. It is produced by heating p-phenetidin with methoxyacetic acid to 248°–266° F; it crystallizes from water in needles with a melting point at 208.4°–210.2° F. Methoxacet-p-phenetidin results according to the equation:

$$CH_3OCH_2COOH+NH_2C_6H_4OC_2H_5=$$
$$=CH_3OCH_2CONHC_6H_4OC_2H_5+H_2O$$

The following considerations gave rise to the production of this substance:

From the investigations of W. Ostwald (Ueber die Affinitætsgrœssen organischer Saeuren, Zeitschrift fuer physikalische Chemie III), it appears that the alkylglycolic acids are remarkably stronger than the glycolic acid itself and manifold stronger than the acetic acid. Thus for instance for Methoxyacetic acid K=0,0335, for acetic acid K=0,00180.

This noteworthy difference between acetic acid and methoxyacetic acid must in any event show itself also in derivatives of these acids, viz: in their condensation products with aromatic bases like anilin, phenetidin, etc. Now there exists in fact between acet-p-phenetidin (**Phenacetin**) and methoxacet-p-phenetidin (**Kryofine**) a great difference in behavior toward saponifying agents. There are for example, saponified in boiling with alcoholic caustic potash solution under circumstances otherwise equal, 10% of Phenacetin and 60% of Kryofine; by means of hydrochloric acid also, phenacetin is saponified with much more difficulty than Kryofine."

Now, as is well known, the acid gastric juice acts as also does the alkali of the duodenum on such substances as a saponifier; there

could therefore appear in some manner a perceptible difference in the behavior of these substances within the organism. It was therefore indicated to investigate Kryofine for antipyretic action.

Kryofine forms white, odorless crystals, which have no taste and are therefor very conveniently taken in powder form. Its solubility in water is 1:52 in boiling and 1:600 in cold water. In concentrated solution Kryofine tastes bitter and biting. At the medical clinic the antipyretic was given exclusively in powder form, and enclosed in wafers.

As a reliably active dose 7½ grains of Kryofine has been ascertained to be sufficient; one achieves therewith a result like with 15 grains of Phenacetin. When the action of Kryofine failed, then Phenacetin, Lactophenin and Antipyrin, which for the sake of comparison were repeatedly used in the same person, remained also almost unexceptionally without influence.

A few examples may be cited out of a great number of investigations. to show the action of Kryofine.

First Case.

Girl, aged 17; severe typhoid fever, fourth week.

Feb. 23-'97	7 a. m. t.	102 9 p.	116
	10 a. m.	102.2	104
	4 p. m.	104.2	108
	8 p. m.	103.3	108
Feb. 24.	7 a. m.	101.7	92
	10 a. m.	101 3	112
	4 p. m.	103 3	116
	8 p. m.	102.2	116
Feb. 25.	7 a. m.	103 1	112
	10 a. m.	101.5	108
	4 p. m.	103.1	108

4 p. m. 7½ grains of Kryofine

	4.45 p. m. t.	101.3 p.	104
	5.55 p. m.	99.5	100
	7 p. m.	98.2	96
Feb. 26	7 a. m.	101.8	100
	10 a. m.	100.6	104

10 a. m. 7½ grains of Kryofine

	11 a. m.	98.6	100
	12 noon	96.8	96
	1 p. m.	98.2	96
	4 p. m.	99.3	96
	7 p. m.	103.1	116

The patient therefor became **entirely free of fever both times after the ingestion of 7½ grs. of Kryofine,** and remained so on the second day for almost twelve hours.

Second Case.

Man, aged 34, Typhoid fever, third week.

Feb. 25-'97.	8 p. m.	t. 103.3	p. 100
Feb. 26.	7 a. m.	103.3	100
	10 a. m.	104.7	104
	4 p. m.	103.1	104
	8 p. m.	103.3	100
Feb. 27.	7 a. m.	102.4	104
	10 a. m.	102.7	100
10.45 a. m. 4 grs. of Kryofine			
	12.15 p. m.	**101.3**	96
	12.30 p. m.	**102.2**	100
	12.45 p. m.	**101.3**	84
	4 p. m.	103.1	116
	8 p. m.	102.6	120
Feb. 28.	7 a. m.	102.6	120
	10 a. m.	103.6	100
	4 p. m.	104.	100
	8 p. m.	102.9	100
Mar. 1.	7 a. m.	103.5	108
	12 noon	101.7	108
	4 p. m.	100.6	108
Mar. 2.	7 a. m.	t. 102.6	p. 104
	10 a. m.	102.2	132
	4 p. m.	103.1	132
	8 p. m.	101.8	108
Mar. 3.	7 a. m.	103.1	100
	10 a. m.	102.9	100
	4 p. m.	103.1	104
	5 p. m.	102.4	104
	6.30 p. m.	102.9	108
6.30 p. m. 7½ grains of Kryofine			
	7 p. m.	**100.6**	96
	7.30 p. m.	**100.8**	96
	8 p. m.	**98.6**	92
	9 p. m.	**99.1**	96
Mar. 4.	**7 a. m.**	**101.8**	100
	10 a. m.	103.6	120
	4 p. m.	103.5	104
	8 p. m.	102.9	112

The patient indeed experienced a slight, transient reduction of temperature after taking 4 grains of Kryofine on February 27, 1897, but did not become entirely free of fever; whereas on March 3, 1897, after 7½ grains of Kryofine the body-temperature sank to 98.6° F., and **even the following morning the action of the Kryofine seemed to be perceptible** in an unusually low febrile temperature.

Third Case.

Female, aged 34, with pleuropneumonia of right upper and middle lobes.

July 20-'96.	Fifth day of sickness		
	8 p. m.	t. 103 6	p. 104
July 21.	7 a. m.	101.7	120
9.30 a. m. 7½ grs. of Kryofine			
	10 a. m.	**100.4**	120
	12 noon	**100.**	112
	1 p. m.	**99.9**	116
	2 p. m.	**98.6**	120
	3 p. m.	**99.1**	112
	4 p. m.	**100.4**	126
	5 p. m.	**101.5**	120
July 21.	6 p. m.	t. 102.4	p. 116
	7 p. m.	103.3	132
	8 p. m.	103.5	124
July 22.	7 a. m.	101.5	108
	10 a. m.	99.7	112
	4 p. m.	100.	104
	8 p. m.	99.3	116
July 23.	7 a. m.	98.8	80
	12 noon	96.6	104
	4 p. m.	96.8	88

Fourth Case.

Midwife, aged 38, with severe puerperal sepsis after neglected abortion.

Nov. 2.'95.	8 p. m.	t. 102.7	p. 142
Nov. 3.	7 a. m.	104.9	152
	12 noon	102.2	142
	4 p. m.	102.9	132
Nov. 4.	7 a. m.	105.3	120
	12 noon	102.4	148
1 p. m. 7½ grs. of Kryofine			
	2 p. m.	**t. 101.7**	**p. 124**
	4 p. m.	**99.**	116
	6 p. m.	**100.**	104
	8 p. m.	**100.**	124
Nov. 5.	7 a. m.	102.7	132
	12 noon	102.2	132
	4 p. m.	102.2	140
	6 p. m.	104.	156

Fifth Case.

Girl, aged 12, with acute febrile hemorrhagic nephritis following scarlet fever.

Nov. 10-'95.	7 a. m.	t. 104.	p. 112
10 a. m. 7½ grs. of Phenacetin			
	12 noon	102 7	124
	7 p. m.	102.7	128
Nov. 11.	7 a. m.	103.3	132
10 to 12 a. m. 7½ grs. of Antipyrin every half hour.			
	12 noon	102.9	100
	7 p. m.	102.7	132
Nov 12.	7 a. m.	102 4	140
10 to 12 a. m. 7½ grs. of Antipyrin every half hour.			
	12 noon	103.1	140
	7 p. m.	102.4	140
Nov. 13.	7 a. m.	103 1	124
	11 a. m.	102.4	112
11 a. m. 7½ grains of Kryofine			
	1 p. m.	**t. 101.3**	p. 120
	3 p. m.	**100.9**	100
	5 p. m.	**101.7**	124
	7 p. m.	**102.**	140
	9 p. m.	102.4	144
Nov. 14.	7 a. m.	103 3	116
	9 a. m.	102.4	148
9 a. m. 7½ grains of Kryofine			
	11 a. m.	**101.5**	140
	1 p. m	102.9	144
	3 p. m.	103.5	124
	5 p. m.	102 9	148
	7 p. m.	102.7	136
Nov. 15.	7 a. m.	103.1	116
	10 a. m.	103 1	140
7½ grains of Phenacetin at 11-12 and 1 o'clock			
	4 p. m.	102.2	116
	7 p. m.	102.2	116

From the above it is apparent that the patient **was almost uninfluenced** in her fever **in spite of large doses of Antipyrin and Phenacetin** whereas **7½ grains of Kryofine brought about a very decided temperature reducing effect.**

Sixth Case.

Servant girl, aged 22 suffering with extensive facial erysipelas.

Nov. 13-'95.	7 p. m.	t. 104.9	p. 112
Nov. 14.	7 a. m.	104.2	108
	10 a. m.	102.6	104
10 a. m. 7½ grains of Kryofine			
	12 noon	**100.9**	100
	2 p. m.	103.5	120
	4 p. m.	104.	120
	6 p. m.	104.4	124
	8 p. m.	104.9	128
Nov. 15.	7 a. m.	104.	112
	11 a. m.	103.3	108
11 a. m. 7½ grains of Kryofine			
	1 p. m.	**100.9**	p. 104
	3 p. m.	**102.6**	112
	5 p. m.	105.8	120
	7 p. m.	105.3	124
	9 p. m.	103 5	112
Nov. 16.	7 a. m.	105.4	124
	10 a. m.	104.4	116
10 a. m. 15 grains of Phenacetin			
	12 noon	102.6	116
	2 p. m.	100 9	108
	4 p. m.	101.5	112
	6 p. m.	102.4	112
	8 p. m.	102.	116

In this case we intentionally changed from Kryofine to Phenacetin to gain a comparison of the effect of both drugs. So long as the course of the disease was at its height, it appeared that Kryofine was **at least equally valuable in effect with Phenacetin, especially when**

one considers that of Kryofine only one-half the dose of Phenacetin had been prescribed.

The number of examples could be increased by a very large figure, but the above observations may suffice to bring the proof that we have in Kryofine a febrifuge which both in effect and in safety of action may very well out-rival the antipyretics in use before this. Let it be further remarked that Kryofine has shown itself efficacious in the fever of consumptives, in streptococcus diphtheria, tubercular meningitis, and ulcerative endocarditis.

Serious collateral effects we have not as yet seen. In a few patients there occurred during the fall in temperature a considerable perspiration. Cyanosis also was occasionally perceptible Whether a slight nausea, of which exceptionally there was complaint, had any connection with the drug, remains as yet undecided.

Frequently the influence of Kryofine on the pulse curve and arterial pressure was observed, for which purpose Dudgeon's sphygmograph was employed to obtain the pulse pictures, and for the determination of arterial pressure the sphygmomanometer of v. Basch was used. It appeared that under the influence of Kryofine the blood pressure in the radial artery rose 10-15 mm. Hg. and that in agreement therewith, an over-dicrotic pulse curve became a completely dicrotic or under-dicrotic one.

In her inaugural dissertation Miss Bach will give a more particular report on the influence of Kryofine on tissue changes.

Following surmise, it was advisable to investigate Kryofine for any effect in relieving pain and in fact it has frequently proven itself a good antineuralgic. In a few cases of recent sciatica its rapid effect was most startling Prominence should be given the fact, that in a man with alcoholic polyneuritis, for whose intense pain sodium salicylate, phenacetin, antipyrin and exalgin had been prescribed without any effect, by means of Kryofine alone a very prolonged relief from pain was effected. The drug was prescribed 7½ grains three times a day.

In acute and chronic articular rheumatism it seemed to us to be less effective but always compared favorably with Phenacetin.

In conclusion, I do not hesitate to recommend Kryofine as a noteworthy and commendable antipyretic and antineuralgic,